Kinesin light chain 1 suppression impairs human embryonic stem cell neural differentiation and amyloid precursor protein metabolism.

Journal: PLoS One

Publication Year: 2012

Authors: Rhiannon L Killian, Jessica D Flippin, Cheryl M Herrera, Angels Almenar-Queralt, Lawrence S B Goldstein

PubMed link: 22272245

Funding Grants: Using Human Embryonic Stem Cells to Understand and to Develop New Therapies for Alzheimer's Disease, Interdisciplinary Stem Cell Training Program at UCSD

Public Summary:
Five and a half million people in the U.S. alone have the disease. It is the sixth leading cause of death in the U.S. Care for the afflicted costs $200 billion annually. A staggering 1 in 8 older Americans U.S. have it. It is Alzheimer Disease, a devastating disease with no cure and no known cause. Scientists suspect the disease is exasperated by abnormal brain deposits of two proteins known as amyloid-beta and tau, but it is not known what causes these proteins to behave aberrantly. Since both of these proteins have uniquely human compositions, their behavior has been challenging to address fully in animal models, although recent work suggests that faulty transport of proteins and other cargos within nerve cells can lead to altered behavior of amyloid beta and tau. Therefore, we used a human model system based on human pluripotent stem cells –cells capable of giving rise to any cell type in the body – to test the notion that impaired transport of materials within nerve cells can lead to abnormal levels of amyloid beta and tau. We generated human pluripotent cells with reduced levels of a protein essential for the transport of many cargos within nerve cells and tested how this affected the production of the nerve cell cultures as well as the levels of amyloid beta and tau. Our results indicate that perturbing transport in this way can impair the production of nerve cells. Further, these nerve cell cultures contain less amyloid beta and tau proteins. Thus we have created a human model system with which to test the role of intracellular transport in any human cell type and have demonstrated that altering intracellular transport can alter levels of amyloid beta and tau in human nerve cells. This human model system will be useful for future studies addressing the possible causes and potential treatments of Alzheimer Disease.

Scientific Abstract:
The etiology of sporadic Alzheimer disease (AD) is largely unknown, although evidence implicates the pathological hallmark molecules amyloid beta (Abeta) and phosphorylated Tau. Work in animal models suggests that altered axonal transport caused by Kinesin-1 dysfunction perturbs levels of both Abeta and phosphorylated Tau in neural tissues, but the relevance of Kinesin-1 dependent functions to the human disease is unknown. To begin to address this issue, we generated human embryonic stem cells (hESC) expressing reduced levels of the kinesin light chain 1 (KLC1) Kinesin-1 subunit to use as a source of human neural cultures. Despite reduction of KLC1, undifferentiated hESC exhibited apparently normal colony morphology and pluripotency marker expression. Differentiated neural cultures derived from KLC1-suppressed hESC contained neural rosettes but further differentiation revealed obvious morphological changes along with reduced levels of microtubule-associated neural proteins, including Tau and less secreted Abeta, supporting the previously established connection between KLC1, Tau and Abeta. Intriguingly, KLC1-suppressed neural precursors (NPs), isolated using a cell surface marker signature known to identify cells that give rise to neurons and glia, unlike control cells, failed to proliferate. We suggest that KLC1 is required for normal human neural differentiation, ensuring proper metabolism of AD-associated molecules APP and Tau and for proliferation of NPs. Because impaired APP metabolism is linked to AD, this human cell culture model system will not only be a useful tool for understanding the role of KLC1 in regulating the production, transport and turnover of APP and Tau in neurons, but also in defining the essential function(s) of KLC1 in NPs and their progeny. This knowledge should have important implications for human neurodevelopmental and neurodegenerative diseases.